

Oncogenes Come of Age

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Mutations of proto-oncogenes are common events in the pathogenesis of cancers, as shown in a wide range of studies during the 30 years since the discovery of these genes. The benefits of novel therapies that target the products of mutant alleles in human cancers, and the demonstrated dependence of cancers in mouse models on continued expression of initiating oncogenes, are especially promising signs that revolutionary improvements in cancer care are possible. Full realization of the promise of targeted therapies, however, will require better definitions of the genotypes of human cancers, new approaches to interrupt the biochemical consequences of oncogenic mutations, and a greater understanding of drug resistance and tumor progression. In this paper, we summarize recent efforts toward these goals in our laboratory and others.

It is now about 30 years since the cellular progenitors of retroviral oncogenes, the first proto-oncogenes, were identified in vertebrate genomes (Stehelin et al. 1976; Rosenberg and Jolicoeur 1997), and over 20 years since mutant versions of such genes were first discovered in human cancers. In the past two decades, the list of mutant proto-oncogenes in human tumors has grown dramatically; many genes belonging to at least two other categories—tumor suppressors and governors of genomic integrity—have been implicated in carcinogenesis, and the proteins encoded by such genes have been extensively characterized. These developments have set the stage for more rational approaches to the detection, diagnosis, classification, treatment, and prevention of human cancers. Yet the most common and most lethal of these diseases are still inadequately controlled with traditional methods (chemotherapy and radiation), which do not take advantage of our new understanding of cancer at the molecular level.

In this survey of recent work from our laboratory and many others, we emphasize evidence that encourages the belief that therapies targeted against the specific genetic damage present in each cancer, especially therapies affecting proteins encoded by mutant proto-oncogenes, are likely to have increasingly prominent roles in future efforts to control cancer. Reaching this objective will require a fuller description of cancer genotypes through a nationally coordinated effort; a better understanding of signaling pathways altered by oncogenic mutations; a deeper picture of interactions among the multiple cancer genes in a single tumor; more drugs and antibodies that counter the effects of such mutations, in part to prevent the emergence of drug resistance; and a more refined description of how tumors progress as a consequence of changes within cancer cells and the microenvironment.

We address these issues by considering mutant proto-oncogenes in several mouse models of human cancers

and, in at least one case, a human disease, adenocarcinoma of the lung. One overriding notion that we stress is the idea that oncogenes are not required simply to initiate and maintain tumor growth; in several contexts, continued expression of mutant oncogenes is required to maintain the viability of the cancer cell. Such “oncogene dependence” provides an important vulnerability that some drugs already in clinical use—most obviously imatinib (Gleevec) and other inhibitors of protein-tyrosine kinases—effectively exploit. Since different types of tumors can be dependent on the same or similar oncogenes, and, conversely, histologically indistinguishable tumors from the same organ often depend on different oncogenes, it is essential that tumor genotypes be precisely and fully determined. We contend that much of contemporary cancer research should now be directed toward defining the molecular targets and therapeutic agents that show promise of producing “imatinib equivalents” for all forms of human cancer.

ONCOGENE DEPENDENCE IN CANCER

Viral Mutants

The idea that cancers are dependent on continued production of an oncogenic protein has its most explicit origin in classic studies of a temperature-sensitive mutant of the *src* gene of Rous sarcoma virus (RSV) (Martin 1970). These experiments not only clearly separated the oncogenic from the replicative functions (genes) of RSV; they also showed that the viral oncogene (*v-src*) was required to maintain as well as to initiate the transformed state.

Transgenic Mice with Inducible Oncogenes

More recent studies with transgenic mice that express oncogenes under the control of regulated promoters have made a dramatic point: After the oncogenes are turned on and tumors emerge, extinction of expression often leads to rapid disappearance of the tumor, as a result of apopto-

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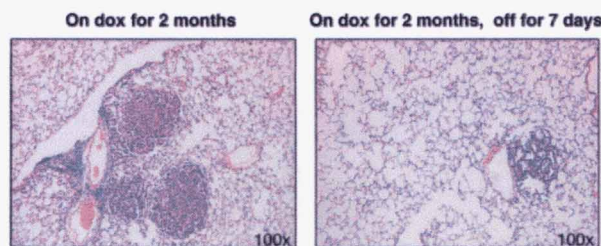
Table 1. Examples of Tumor Maintenance in Mouse Models

Tumor type	Oncogene	Mechanism of regression	Reference
Melanoma	<i>H-ras</i>	<i>Ink4a/Arf</i> and VEGF independent; apoptosis in tumor cells and host-derived endothelial cells; decreased proliferation; not immune-related	Chin et al. (1999)
T-cell lymphoma/acute myeloid leukemia	<i>Myc</i>	differentiation, proliferative arrest, and apoptosis in tumor cells	Felsher and Bishop (1999)
Osteosarcoma	<i>Myc</i>	differentiation in tumor cells	Jain et al. (2002)
Mammary	<i>Myc</i>	unknown	D'Cruz et al. (2001)
Mammary	<i>Neu</i>	apoptosis and decreased proliferation in tumor cells	Moody et al. (2002)
Mammary	<i>Wnt</i>	unknown; p53 independent	Gunther et al. (2003)
Pancreatic beta-cell	<i>Myc</i>	apoptosis, redifferentiation, decreased proliferation in tumor cells and vascular degeneration; occurs despite presence of <i>Bcl-x_L</i> ; p19 ^{Arf} and p53 independent	Pelengaris et al. (2002); G.I. Evans (unpubl.)
Non-small-cell lung cancer	<i>K-ras</i>	apoptosis (<i>Ink4A/Arf</i> and p53 independent) and decreased proliferation in tumor cells	Fisher et al. (2001)
Non-small-cell lung cancer	<i>EGFR</i>	unknown	K. Politi et al. (in prep.)
Sarcoma	<i>K-ras</i>	apoptosis and decreased proliferation in tumor cells; p53 independent; T-cell independent	Pao et al. (2003)
Leukemia	<i>Bcr-abl</i>	apoptosis in tumor cells	Huettner et al. (2000)
Skin	<i>Myc</i>	growth arrest and irreversible differentiation	Flores et al. (2004)
Hepatocellular carcinoma	<i>Myc</i>	differentiation	Shachaf et al. (2004)
Hepatocellular carcinoma	<i>Met</i>	apoptosis and decreased proliferation in tumor cells	Wang et al. (2001)

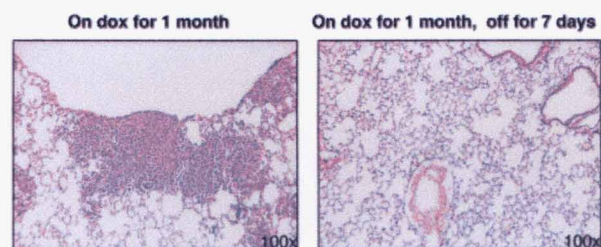
sis, differentiation of the cancer cells, or disappearance of vascular endothelial cells (Table 1). For example, about 5 years ago, our group constructed mice in which a mutant transgenic form of the Kirsten *Ras* gene (*K-Ras^{G12D}*) is regulated by a tetracycline-dependent transcription factor encoded by a second lung-specific transgene (Fisher et al. 2001). Using this system *K-Ras^{G12D}* is expressed in the lung at levels similar to the endogenous normal *K-Ras* gene, when a tetracycline analog, doxycycline, is provided in the diet. Lungs from such animals appear normal, and the mutant transgene is silent in the absence of

the antibiotic. If the mice are maintained on doxycycline, foci of hyperplastic cells appear throughout the lung fields after about a month; by 2–3 months of doxycycline administration, adenomas and adenocarcinomas appear at multiple sites. If, however, doxycycline is then withdrawn, levels of mutant *K-Ras* RNA (and presumably protein) fall precipitously, and the tumor cells display signs of programmed cell death; as a result, the tumors disappear within 3–7 days, as judged by magnetic resonance imaging or by histopathology, and do not recur in the absence of drug (Fig. 1A).

A WT background



B *Ink4a/Arf*^{-/-} background



Bitransgenic *TetO-Kras^{G12D}/CCSP-rtTA* Mice

Figure 1. Oncogenic *K-ras* is required for lung tumor maintenance with or without loss of tumor suppressor genes. Samples of lung tissue, stained with hematoxylin and eosin, after exposure to doxycycline for 1 or 2 months and after withdrawal for 7 days are shown (Fisher et al. 2001). Withdrawal of doxycycline leads to rapid tumor regression in bi-transgenic *CCSP-rtTA/TetOKras^{G12D}* in a wild-type (WT) background (A) and in an *Ink4A/Arf*-deficient background (B). Similar results were obtained in a *p53*-deficient background (Fisher et al. 2001). Magnification, 100x.

To ask whether this apparent oncogene dependence occurs only in the absence of other oncogenic mutations, we repeated the experiments in mice known to be deficient in the tumor suppressor genes *p53* or *Ink4a/Arf*. Under these conditions, adenocarcinomas appeared more rapidly, usually within a month after doxycycline induction, but again quickly regressed by an apoptotic mechanism when the doxycycline was withdrawn (Fig. 1B). Thus, dependence of the mouse lung adenocarcinomas on the initiating *K-Ras* oncogene is not relieved by additional mutations in important tumor suppressor genes.

Our *K-Ras*-dependent lung cancer model and many of the other doxycycline-inducible mouse models listed in Table 1 prompt a general comment about oncogene dependence. It seems from these studies that cells that were at one time fully viable in the absence of the product of each inducible oncogene have become "imbalanced" in some way, so that sudden deprivation of the oncogene product now triggers an event—apoptosis, differentiation, or loss of angiogenic signals—that leads to tumor regression. Understanding such imbalances and their consequences could offer new ways to interfere with signaling downstream of an oncogenic activity. Particularly in the case of *RAS* genes, which are mutant in about a third of human tumors but for which no effective targeted inhibitor has been found, such insights might be an important step toward improving therapies of common human cancers.

Cancer Therapies in Patients

An example of dramatically improved therapy for a human cancer underscores the importance of the concept of oncogene dependence. As discussed elsewhere (see Sawyers, this volume), the use of imatinib—a potent inhibitor of at least three protein-tyrosine kinases, including ABL (and its mutant form BCR-ABL)—for the treatment of chronic myeloid leukemia (CML), a leading form of adult leukemia, rapidly reverses the hematological and symptomatic manifestations of the disease and maintains remissions for up to 5 years and more, especially when therapy is begun during early stages of the disease (for review, see Deininger et al. 2005). The appearance of second-site mutations in the kinase domain of BCR-ABL that confer imatinib resistance (Gorre et al. 2001) constitutes powerful evidence that the drug response is indeed due to the dependence of the leukemic cells on mutant ABL kinase activity. Strategies based on these mutations are now being pursued to prevent or overcome drug resistance (Shah et al. 2004; Burgess et al. 2005; Carter et al. 2005; Gumireddy et al. 2005; Sawyers, this volume).

Several other human cancers, including solid tumors, bearing changes in *ABL*—or mutations in the other two genes, *CKIT* and *PDGFR-A*, encoding kinases known to be inhibited by imatinib—also respond to this drug. This strengthens the argument that oncogene dependence is a general phenomenon, affecting solid and liquid cancers. Thus, therapeutic responses in human patients, not just regulated expression of transgenes in mice or temperature-sensitive mutant oncogenes in cell culture, provide important evidence for oncogene dependence.

EVIDENCE FOR EGFR ONCOGENE DEPENDENCE IN HUMAN LUNG ADENOCARCINOMA

Two small chemical inhibitors of the EGFR tyrosine kinase, gefitinib (Iressa) and erlotinib (Tarceva), were tested for efficacy in human lung cancer for several years (Fukuoka et al. 2003; Kris et al. 2003) before it was recognized that some lung cancers carry dominantly acting mutations in the *EGFR* gene (Lynch et al. 2004; Paez et al. 2004; Pao et al. 2004). The recent discovery of such *EGFR* mutations offers a striking example of how drug responses in patients can reveal dependence of cancers on a mutant oncogene.

Non-small-cell lung cancer (NSCLC) is the leading cause of cancer death worldwide (Parkin et al. 2005). In about 10% of patients in the U.S. and Europe with adenocarcinoma of the lung, the most common form of NSCLC, rapid partial remissions occur when these drugs are used, even late in the course of metastatic disease, and in parts of Asia the response rate is significantly higher (Fukuoka et al. 2003; Kris et al. 2003). Sometimes (as shown in Fig. 2A) the response is dramatic, resembling the tumor regression seen in our *K-Ras*-based mouse model of lung cancer when doxycycline is withdrawn (Fisher et al. 2001).

Observations like these suggested that the two tyrosine kinase inhibitors (TKIs) might be inactivating mutant kinases, either the known target for these drugs, EGFR, or some other unsuspected protein-tyrosine kinase among the 90 encoded in the human genome (Manning et al. 2002). Sequencing of the coding exons of *EGFR* genes in tumors that showed radiographic responses to the TKIs revealed that sensitivity to gefitinib and erlotinib were highly associated with mutations in the *EGFR* kinase domain (Lynch et al. 2004; Paez et al. 2004; Pao et al. 2004; see Thomas et al.; Haber et al.; both this volume). (For an example, see the computerized tomography scans in Fig. 2B.) Surprisingly, these mutations are highly idiosyncratic: Nearly 90% are either point mutations that change leucine at position 858 to arginine (L858R) or three- to seven-codon deletions affecting the highly conserved sequence, LREA, that is positioned close to the ATP-binding site in the kinase domain (for review, see Pao and Miller 2005).

The biochemical, physiological, and structural consequences of these mutations and several other substitution mutations that have been associated with TKI responsiveness are still under study (Sordella et al. 2004; Tracy et al. 2004; Amann et al. 2005; Engelman et al. 2005; Greulich et al. 2005; Chen et al. 2006), but several observations support the idea that this subset of lung adenocarcinomas is dependent on the mutant EGFR kinase. The mutations are strongly associated with a measurable radiological response to the TKIs; such responses are rarely observed in tumors without detectable *EGFR* mutations, including the 20–30% of tumors with mutations in *KRAS* (Eberhard et al. 2005; Pao et al. 2005b), the product of which acts "downstream" of EGFR. In addition, second-site mutations in one of the exons encoding the EGFR kinase domain are observed in about half of drug-resistant tumors that resume growth during treatment with the

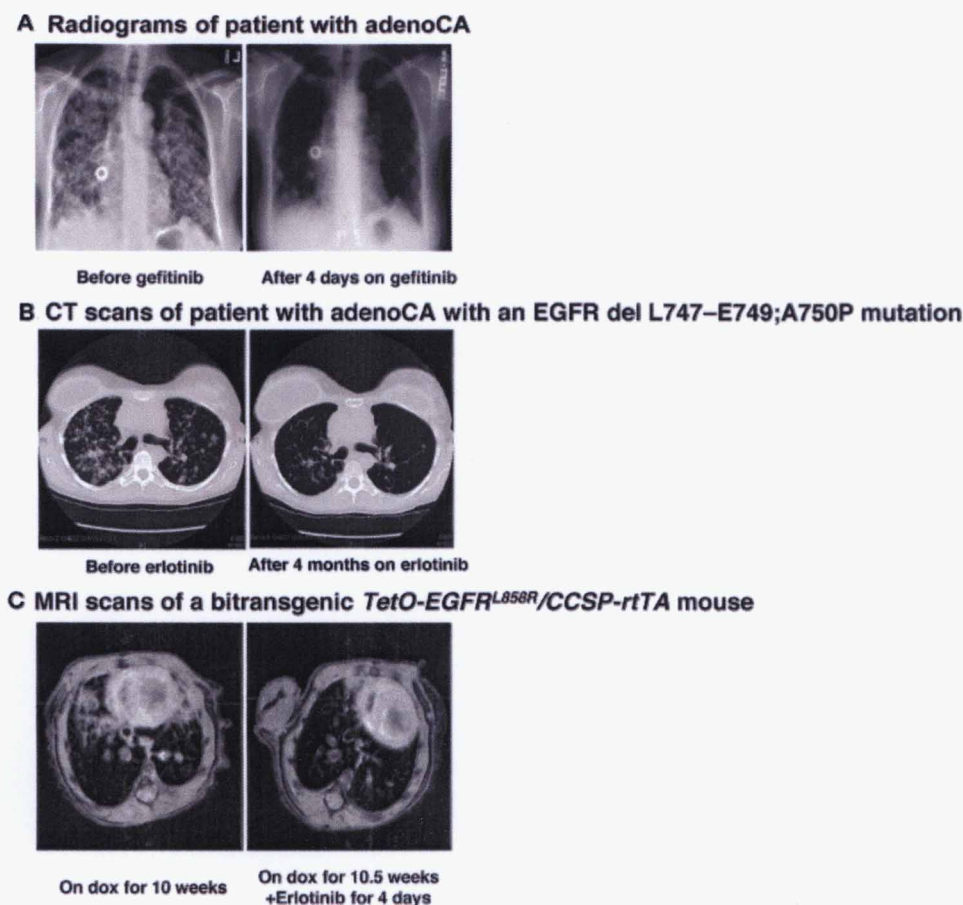


Figure 2. Lung tumors with *EGFR* mutations respond dramatically to treatment with tyrosine kinase inhibitors. Chest radiographs (A) and chest computerized tomography-generated images (B) showing a tumor response to gefitinib (A) after 4 days of treatment and erlotinib (B) after 4 months of treatment in two patients, one of which is known to have a tumor with an *EGFR* mutation. (C) Magnetic resonance images of lungs from a mouse expressing the *EGFR* L858R mutant before (left panel) and after 4 days (right panel) of erlotinib treatment.

TKIs (Kobayashi et al. 2005; Pao et al. 2005a).

Strikingly, these resistance-inducing secondary *EGFR* mutations all encode the same change, threonine to methionine at position 790, a change that is strictly analogous to one of the mutations observed in imatinib-resistant forms of *BCR-ABL*, *CKIT*, and *PDGFR-A* in various types of tumors treated with imatinib (Gorre et al. 2001; Cools et al. 2003; Tamborini et al. 2004; see Sawyers, this volume). The introduction of a bulky side chain in the methionine residue is likely to interfere with drug binding; screening of additional TKIs for their ability to bind to or inhibit the doubly mutant kinases have already identified agents that are effective in the presence of T790M and analogous mutations (Carter et al. 2005; Kwak et al. 2005); such drugs might be used after primary resistance occurs or in combination with the first TKI to prevent the emergence of resistance.

As described elsewhere (see Hillan et al., this volume), long-term outcomes of gefitinib or erlotinib treatment of *EGFR*-mutant tumors, as measured by survival or by time to tumor progression, are not as good as those observed in the treatment of CML with imatinib. Although a full explanation of these disappointing results is not yet at hand, the emergence of drug resistance, generally within a year

of commencing therapy, is likely to be part of the problem and may be alleviated by the use of additional TKIs. The relatively modest effects of TKIs on survival may also reflect the use of these drugs relatively late in the course of the disease, a phase more akin to the blast crisis than the early stages of CML, so that other oncogenic mutations may dampen the therapeutic efficacy. Consistent with this idea, partial rather than complete radiographic responses to the TKIs are commonly seen in patients with metastatic NSCLC. From this perspective, treatment of early-stage disease (e.g., adjuvant therapy with TKIs at the time of surgery) or first-line treatment of advanced disease with TKIs might have more potent effects on survival.

Some tumors with increased copy numbers of wild-type *EGFR*, as determined by fluorescent in situ hybridization, appear to be sensitive to treatment with gefitinib, since at least one group has reported a stronger correlation of the outcome, especially survival, with *EGFR* gene amplification than with *EGFR* mutation (Cappuzzo et al. 2005). Similar results have been described with erlotinib (Tsao et al. 2005). It will be important to confirm these findings in additional, larger studies and, if they prove valid, to understand how TKIs produce benefit in this situation.

MOUSE MODELS OF EGFR-DEPENDENT LUNG CANCER

Building mouse models of lung cancer is a useful means to characterize the dependence of lung adenocarcinomas on mutant *EGFR*, to study the mechanism of tumor induction and regression, to test candidate therapies, and to investigate mechanisms of drug resistance. To those ends, we have produced a series of transgenic mice that encode wild-type *EGFR*, L858R *EGFR*, and an LREA deletion form of *EGFR* under the control of a doxycycline-responsive regulatory system (K. Politi et al., in prep.). Induction of the L858R mutant form of *EGFR* leads to development of diffuse lung tumors comprising cells expressing markers of type II pneumocytes and highly reminiscent of human bronchioalveolar carcinoma, followed by the appearance of multifocal adenocarcinomas. The tumors rapidly regress, as observed by magnetic resonance imaging or histopathology, when the animals are deprived of doxycycline or when they are treated with erlotinib (Fig. 2C), demonstrating that the tumors are dependent on continued production or activity of the mutant *EGFR*. A detailed description of these lines and others, and their responses to induction and de-induction of *EGFR* and to drugs, will be published elsewhere (K. Politi et al., in prep.).

WHAT IS LIMITING THE IMPACT OF THE MOLECULAR UNDERSTANDING OF CANCER ON PATIENT CARE?

The widespread evidence for oncogene dependence in mouse models and human tumors and the results of treatment of some human cancers with TKIs, especially imatinib, provide strong grounds for optimism about controlling cancer more effectively in the future. Yet the outcomes of most efforts to treat the common cancers have not changed significantly over the past several decades. Why is this? And what is impeding more dramatic change?

Defining Cancer Genotypes

Despite the remarkable growth of knowledge about genes that have been implicated in carcinogenesis, we

still have a very meager picture of the genotype of most of the 50 or more types of human cancer. For many cancer types, some proto-oncogene or tumor suppressor gene is known to be aberrant (subtly mutated, deleted, rearranged, amplified, or epigenetically modified). However, when studied intensively, most tumors appear to have multiple altered cancer genes. Furthermore, tumors that are histologically indistinguishable are often genetically different, and important elements in the clinical history, such as occupational exposures or never smoking, sometimes correlate more strongly than histology with the tumor genotype.

Consider, for example, the situation with lung adenocarcinoma, one of most common and lethal human cancers. About a quarter of such tumors have a mutant copy of *KRAS*, and this occurs nearly exclusively in smokers (Ahrendt et al. 2001). Similarly, we now know that about 10% have a mutant copy of *EGFR*, mainly in "never smokers" (Pao et al. 2004). In addition, small numbers of tumors have mutations in genes that encode other components of the growth factor signaling network: *ERBB2*, *BRAF*, and *PIK3CA* (see Fig. 3) (Brose et al. 2002; Naoki et al. 2002; Samuels et al. 2004; Stephens et al. 2004; Shigematsu et al. 2005). Interestingly, mutations in more than one of these genes are rarely encountered in a single tumor, implying that no further selective advantage is conferred by additional lesions affecting this signaling network. However, the combined percentage of tumors known to have even a single mutation in this network is relatively small; thus, a mutant oncogene that might provide a therapeutic target has not been identified in the majority of lung adenocarcinomas (Fig. 3). Furthermore, although loss of tumor suppressor genes, especially *P53* and *INK4A/ARF*, is known to occur at high frequency in such tumors (for review, see Forgacs et al. 2001), the influence of tumor suppressor deficiencies on treatment outcomes in the context of specific oncogenic mutations is not known, nor is the effect of mutations in additional proto-oncogenes, as discussed further below.

The development of high-throughput methods for assessing mutations, changes in DNA copy number, and even epigenetic changes provides an opportunity to repair, at least partially, our deficient knowledge of tumor genotypes. The National Institutes of Health is now considering a coordinated, long-term effort to find many of

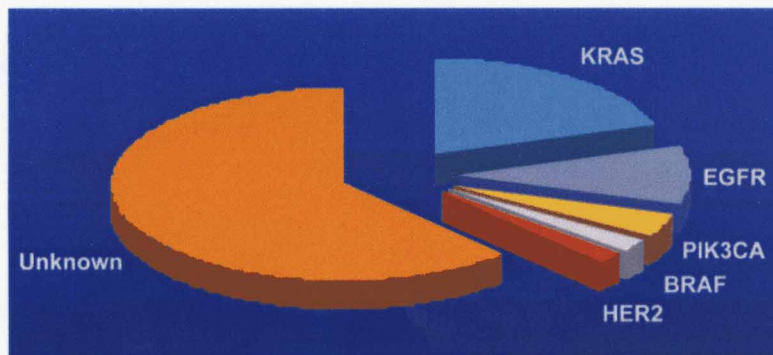


Figure 3. Pie chart depicting the frequency of known proto-oncogenes found to be mutated in non-small-cell lung cancers. As discussed in the text, these genes all encode components of the EGFR signaling network.

the genotypic changes that occur with at least 5% frequency in the 50 or so major types of human cancer (the NCAB Report can be found at <http://www.genome.gov/Pages/About/NACHGR/May2005NACHGRagenda/ReportoftheWorkingGrouponBiomedicalTechnology.pdf>). Preliminary efforts at several centers to determine genotypes, mainly by re-sequencing the coding exons of genes encoding kinases, have yielded interesting results (Bardelli et al. 2003; Samuels et al. 2004; Davies et al. 2005; Parsons et al. 2005; Stephens et al. 2005; see Futreal et al., this volume), but the findings are not yet on a scale adequate to describe the molecular basis of human cancer in the way that will be required for major therapeutic advances.

Finding Novel Inhibitors of Mutant Oncogenes

A second obstacle to greater clinical impact of molecular oncology is the relative paucity of tools that affect potential therapeutic targets other than protein-tyrosine kinases (mostly inhibited by small compounds) or transmembrane proteins and their ligands (mostly blocked by monoclonal antibodies). As noted earlier, this deficiency is especially acute in relation to *RAS* mutants, but applies also to a wide range of oncogenic proteins. Thus far, nearly all beneficial therapies have been targeted against the products of mutant genes, but it seems reasonable to assume that nonmutated components of affected signaling pathways—for example, proteins phosphorylated by tyrosine kinases—will also prove to be vulnerable to attack.

It also seems likely to be important to understand the alterations that are responsible for the “imbalance” in cell signaling responsible for the phenomenon of oncogene dependence. For example, the apoptotic response that is observed when oncogenes are down-regulated in mouse models is presumably blocked in cancer cells expressing oncogenes by proteins induced by the oncogenes. Such proteins might be attractive therapeutic targets, especially when the mutant oncoprotein itself is refractory to inhibition by small molecules.

Minimizing Resistance to Targeted Cancer Therapies

Just as drug resistance is a problem in conventional chemotherapy and in treating infectious diseases, it is already apparent that cancer therapies targeted against known proteins will eventually encounter significant resistance. The encouraging news is that such resistance is usually attributable to secondary mutations affecting the target protein—a situation that permits rational approaches to overcoming resistance through drug screens and protein design. The goal is to develop combination therapies, not unlike those now in wide use for the treatment of HIV/AIDS, which greatly diminish the probability that resistant clones of cancer cells will emerge by genetic selection.

Coping with Mutations in Multiple Proto-oncogenes

Most human cancers, if not all, are the products of multiple genetic changes, but we do not yet have a full account

of the impact of additional oncogenic mutations on a tumor's dependence on any single oncogene. Recent studies of mouse tumor models from Lewis Chodosh and his colleagues indicate that oncogene dependence (for instance, dependence of a mouse mammary tumor on a *Myc* transgene) can be abrogated by secondary mutations in other genes, such as endogenous *Ras* genes (D'Cruz et al. 2001).

These observations have stimulated us to seek secondary spontaneous mutations in mammary tumors arising in tumor-prone transgenic mice. One attractive feature of these experiments is that the detection of a secondary mutation by DNA sequencing implies that it has conferred a selective growth advantage, otherwise it would not be present in a large enough percentage of tumor cells to permit detection by sequencing of unfractionated tumor DNA. In this way, we have shown that secondary mutations in *H-Ras* are encountered in about half of breast tumors induced by an MMTV-*Wnt1* transgene (Podsypanina et al. 2004). Such mutations are not found in tumors induced by an MMTV-*Neu/ERBB2* transgene; this is presumably so because *Ras* proteins act in the same growth factor signaling pathway, and thus, mutants would confer no growth advantage. *Ras* mutations are also not found in the tumors that rapidly appear in bi-transgenic mice, expressing both *Wnt1* and *Neu/ERBB2*. Unexpectedly, however, the *Wnt1* transgene removes the selective pressure for the secondary mutations in the *Neu/ERBB2* gene that commonly enhance kinase activity in tumors arising in mono-transgenic mice (Siegel et al. 1994; Podsypanina et al. 2004). Also unexpectedly, *Ras* mutations do not occur in MMTV-*Wnt1* tumors when they are induced in *p53*-deficient mice. An understanding of these genetic interactions could help to predict which mutant cancer genes are likely to coexist in tumors and which might be the best targets for therapeutic intervention.

Additional insight into the interactions among mutant cancer genes can be obtained by expressing two or more transgenic oncogenes, at least one of which can be transcriptionally controlled. For example, we have built transgenic mice that express *Myc* and mutant *H-Ras* in mammary epithelium, with one or the other under the control of doxycycline, in order to determine whether oncogene dependence of ensuing tumors pertains to one gene, both, or neither with this genetic combination (K. Podsypanina et al., unpubl.).

Assessing Tumor Progression

Approaches to targeted therapy remain limited by a poor understanding of metastasis, invasion, and angiogenesis—the aspects of tumor progression that are responsible for the lethal effects of most tumors. Several papers address these issues (see Egeblad et al.; Bissell et al.; Courtneidge et al.; G.P. Gupta et al.; all this volume; D. Hanahan; J.S. Brugge; both unpubl.). We have developed a novel experimental system in which the progression of phenotypes in a well-characterized model of pancreatic islet cell tumors (Hanahan 1985) can be used to measure the effects of genes (or inhibitory RNAs) that

have been introduced into islet cells by cell-specific infection with retroviral vectors. In this strategy, bi-transgenic mice in which the rat insulin promoter drives production of the SV40 T antigen (RIP-Tag) and the avian retrovirus subgroup A receptor (RIP-TVA) are infected with avian RCAS vectors encoding a variety of factors that might influence tumor progression. Early results suggest that two suspected progression factors, an anti-apoptotic protein (Bcl-xL) and a dominant-negative version of E-cadherin (Naik et al. 1996; Perl et al. 1998), each accelerate the formation of islet cell tumors with invasive properties (Y.-C.N. Du et al., unpubl.).

CONCLUSIONS

As demonstrated in many papers in this volume, cancer research has progressed rapidly over the past three decades and is now well-positioned to contribute powerfully to the control of human cancer. However, the long-anticipated benefits for patients have appeared only recently and in limited sectors of clinical oncology. A more deliberate effort to catalog and comprehend the mutations that afflict all the common human cancers, and more innovative approaches to therapeutic development will now be required to achieve the long-range goals of molecular oncology.

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